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Effect of Famotidine and Diclofenac on Theophylline Pharmacokinetics in the Rabbit

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The aim of this investigation is to study drug interaction between theophylline-famotidine and theophylline-diclofenac in New Zealand white male rabbits. The serum concentration-time profile and the pharmacokinetics parameters of theophylline given alone intravenously (10 mg/kg) and following pre-treatment with either oral famotidine (5 mg/kg) or intramuscular diclofenac (5 mg/kg) were calculated. Theophylline serum concentrations in the rabbit were measured by radio-immunoassay and the pharmacokinetics parameters were computed using the computer program PKCALK. There were no statistically significant changes in the area under the plasma concentration-time curve, half life, clearance, volume of distribution or the mean residual time before and after famotidine or diclofenac pre-treatment. It is concluded that famotidine and diclofenac did not alter the pharmacokinetics of theophylline in the rabbits.

Key Words: Famotidine, Diclofenac, Theophylline, Pharmacokinetics, Drug interaction.

INTRODUCTION

The use of more than one drug in the treatment of patients with various diseases is a common practice in clinical medicine. Although this is sometimes helpful, it may have a risk of altering the actions of the drugs used in combination by either decreasing the effects or leading to a dangerous toxic reaction. This is particularly important when one drug with low therapeutic index is co-administered with a drug that can interfere with its absorption, distribution or elimination[1]. Theophylline is a bronchodilator that is commonly used in the treatment of obstructive pulmonary diseases[2]. It has a narrow therapeutic index that implies a failure of its effect or appearance of toxicity with a little change in its serum level[3]. Theophylline is metabolized mainly by the hepatic microsomal mixed function oxidase (MFO) system[4], and many drugs which interfere with MFO system either

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by inhibiting or increasing the activity may alter the pharmacokinetics of theophylline[3].

Histamine H_2-receptor blocking agents are widely used drugs in the treatment of peptic ulcer disease[5–7]. A large number of studies investigated the interactions between cimetidine (the first H_2-receptor blocker used in clinical practice) or ranitidine and theophylline[8–11]. The majority of these studies have demonstrated that cimetidine, in contrast to ranitidine, increases the serum concentration, prolongs the half life of elimination and reduces the clearance of theophylline. Famotidine is a newer H_2-receptor blocking agent commonly used in the treatment of acid-related disorders[5, 6, 12]. It has a duration of action that is longer and an effective plasma concentration that is lower than that of cimetidine and ranitidine[5, 13]. The famotidine-theophylline drug interaction is not clear. While some studies showed that famotidine did not alter the pharmacokinetics of theophylline[9, 14–16], others demonstrated a substantial decrease in theophylline elimination, a profile similar to that of cimetidine[17].

The use of non-steroidal anti-inflammatory drugs (NSAID) such as diclofenac sodium in the treatment of rheumatic and non-rheumatic disorders has been increased considerably[18–21]. Diclofenac is a NSAID used commonly in treating diseases associated with pain and inflammation[20, 22]. It is a potent anti-inflammatory, analgesic, antipyretic agent and acts by inhibiting cyclo-oxygenase and modulating the release of arachidonic acid[23, 24]. Smilar to other NSAIDs, it causes gastrointestinal disturbances[25, 26]. Many patients on theophylline therapy may receive diclofenac to relieve their arthritic pain.

This study is designed to investigate the potential drug interaction between theophylline famotidine and theophylline-diclofenac using a rabbit as an experimental animal.

EXPERIMENTAL

Animals

The experimental protocols were approved by the research committee at Jordan University of Science and Technology. Two groups of seven New Zealand white male rabbits (2–3 kg) were used in a double blind cross over design. Prior to the experiment day, animals were allowed only water *ad libitum* overnight. During the experiment, animals were allowed to move freely in standard rabbit cages except during drug administration and blood sampling where they were placed individually in a wooden restraining box. Each rabbit was used twice; on one occasion it was given theophylline alone and on other occasion, it was given either famotidine or diclofenac using the following protocol. In the first group, the rabbits received theophylline alone and on other occasion, they received theophylline with famotidine. In the second group, the rabbits received theophylline alone and on other occasion they received theophylline with diclofenac. The sequence of the two treatments was randomized and they were separated by at least two weeks.

Experimental Procedure

Animals were given theophylline (10 mg/kg) using aminophylline B.P. 250 mg/10 mL ampoules (Kamfarma S.R.L., Pisa, Italy) through one of the marginal veins in one of the ears over a period of five minutes. Blood samples (2 mL) were collected from the other marginal veins of the other ear after making a small incision using a local anesthetic as a spray. Blood was collected in a plain tube prior to drug administration and at 15, 30, 60, 90, 120, 180, 240, 300 and 390 min, 23 and 25 h following theophylline administration. Following clot retraction, blood was centrifuged at 1,000 g for 10 min, then serum was collected and stored at –60°C pending analysis. The same procedure was repeated on different occasions 30 min following the administration of 5 mg/kg of famotidine tablets dissolved in distilled water (2 mg/mL solution) orally by gastric intubation (famotidine 40 mg tablets, Medochemie Ltd, Limassol, Cyprus). In the second group of animals, theophylline was given intravenously as described above in first occasion and the same procedure was repeated 30 min following the administration of diclofenac (5 mg/kg) as diclofenac sodium (Voltaren 75 mg/3 mL vial, Ciba-Geigy Limited, Basle, Switzerland) intramuscularly in thigh muscles. The blood was collected as described above. Theophylline serum concentrations were measured by radio-immunoassay (RIA) using a commercially available kit (Coat-a-count kit, Diagnostic Products Corporation, Los Angeles, California, U.S.A.). Samples were run in duplicate. The sensitivity of the assay was 0.2 μg/mL. The inter- and intra-assay coefficients of variation were 7 and 5% respectively.

The effects of famotidine and diclofenac on theophylline kinetics were assessed from the analysis of serum theophylline concentration-time profiles. Pharmacokinetics parameters were computed using the computer program PKCALK[27].

Statistical analysis

Data were expressed as mean ±S.E.M. Statistical analysis was performed using one-way analysis of variance (ANOVA) and Student paired T-test with Bonferroni adjustment as appropriate. P value of < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The serum concentration-time profiles for theophylline given alone and in combination either with famotidine or diclofenac are shown in Figs. 1 and 2 respectively. The pharmacokinetics parameters of theophylline given alone and co-administered with famotidine or diclofenac are summarized in Table-1. Famotidine and diclofenac did not significantly alter the pharmacokinetics parameters of theophylline including half life, area under the plasma concentration-time curve, volume of distribution, clearance and the mean residual time.

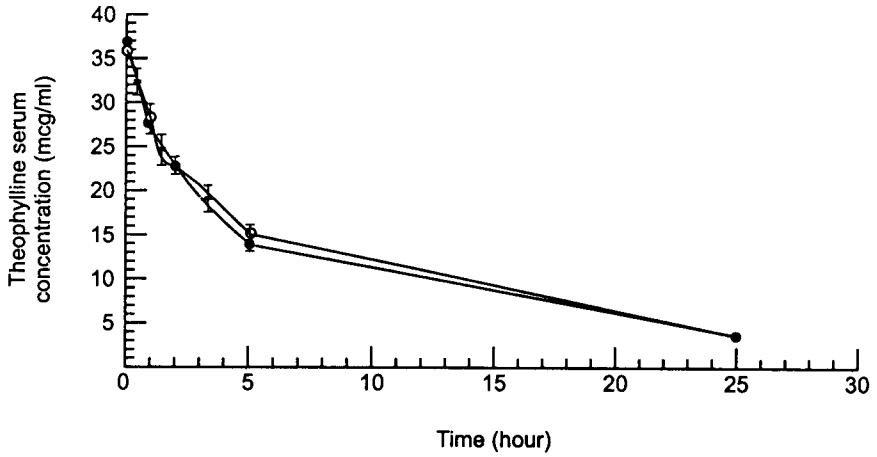

Fig. 1. The serum-concentration profile for intravenous theophylline (10 mg/kg) given alone (open circles) and following famotidine (5 mg/kg) given orally (closed circles) Data are mean ± SEM of 7 values.

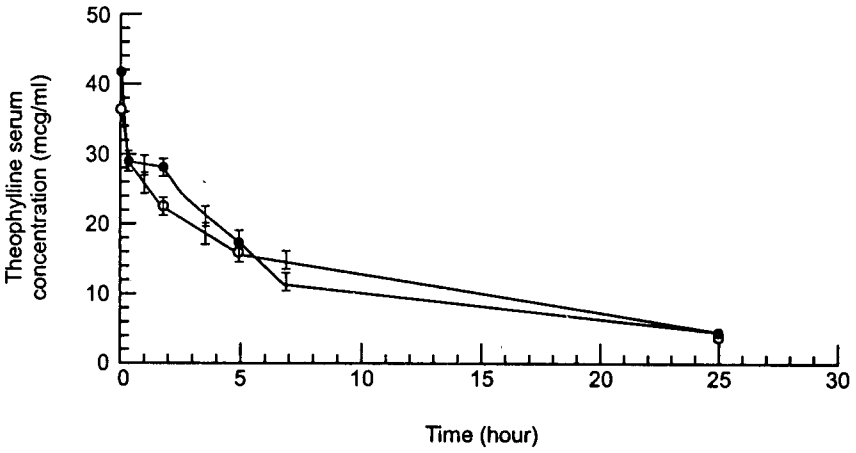

Fig. 2. The serum-concentration profile for intravenous theophylline (10 mg/kg) given alone (open circles) and following diclofenac (5 mg/kg) given intramuscularly (closed circles). Data are mean ± SEM of 7 values.

The present study clearly demonstrates that the pharmacokinetics parameters of theophylline in rabbits are not significantly altered by pre-treatment with either famotidine or diclofenac as already demonstrated in Figs. 1 and 2 and Table-1. It is well known that theophylline is metabolized in humans and animals by multiple forms of cytochrome P-450 enzyme system to several metabolites[2, 28, 29]. Studies indicate some differences between H_2-receptor antagonists with respect to their effects on theophylline pharmacokinetics[16, 30–32]. It is well known that cimetidine influences the pharmacokinetics of theophylline by a prolongation in the half-life, a reduction in clearance and a rise in serum concentration of theophylline[9–11, 14, 33, 34]. This effect is probably due to inhibition

or binding of the imidazole ring of cimetidine to cytochrome P-450 enzyme system and a production of a stable cytochrome-substrate complex, which prevents the access of other agents to cytochrome P-450. In contrast to cimetidine, ranitidine was found to have no significant effect on the pharmacokinetics of theophylline[31, 32].

TABLE-1
PHARMACOKINETICS PARAMETERS OF THEOPHYLLINE (10 mg/kg) ADMINISTERED ALONE INTRAVENOUSLY (CONTROL) AND FOLLOWING FAMOTIDINE (5 mg/kg) ORALLY OR DICLOFENAC (5 mg/kg) INTRAMUSCULARLY

Kinetic parameter*	Control theophylline	Group I famotidine treatment	Group II Pre-diclofenac pre-treatment
K_{el} (h^{-1})	0.05 ± 0.057	0.05 ± 0058	0.037 ± 0.042
$T_{1/2}$ (min)	440 ± 112	461 ± 174	396 ± 65
AUC (μg mL min)	17464 ± 3412	15970 ± 8153	16542 ± 2905
Cl (mL/min/kg)	0.890 ± 0.19	1.19 ± 0.621	0.930 ± 0.14
V_d (mL/kg)	545 ± 76	699 ± 280	521 ± 63
MRT (min)	596 ± 17	598 ± 220	534 ± 92

*Each value represents mean ± SEM of determination in 7 rabbits.

Famotidine is a guanidinothyazole derivative[9], which has rapidly gained acceptance, not only because of its ability to inhibit acid secretion, but also because of its relatively low drug interaction potential[5]. It is a weak inhibitor of drug metabolism *in vivo* in accordance with its low binding affinity to cytochrome P-450 enzymes[35, 36]. It seems that chemical structure can affect the pharmacokinetics and the drug interaction potential of any Hz-receptor antagonist[37]. Mojaverian *et al.*[9] had examined the effects of cimetidine and famotidine on single dose of theophylline pharmacokinetics in rats and showed that famotidine did not alter the pharmacokinetics parameters of theophylline. This was confirmed by studies in normal volunteers[14], and in patients with chronic obstructive pulmonary diseases[15, 16]. However, conflicting results reported by Dal Negro *et al.*[17] demonstrated that famotidine decreased theophylline elimination in a fashion similar to cimetidine in patients with peptic ulcer and chronic obstructive lung diseases.

Diclofenac did not also alter the pharmacokinetics parameters of theophylline in rabbit. It is known that diclofenac, a phenylacetic acid derivative[38] undergoes extensive hepatic metabolism by conjugation to produce five metabolites and is eliminated mainly by hydroxylation and excretion of glucuronide and sulphate conjugates of the metabolites[39–42]. It is known that theophylline is bound to plasma protein in varying degrees[29]. Despite being highly protein-bound, dictofenac has not been observed to alter the pharmacokinetics of other highly protein-bound such as tolbutamide, prednisolane, salicylic acid and did not result in significant changes in dosage requirement in patients receiving oral anticoagulant[39, 40, 43]. Other NSAID such as piroxicam was not found to alter the kinetics of theophylline in healthy men volunteers[44]. Sulfinpyrazone, the phenylbutazone

analogue is an inhibitor of the metabolism of warfarin, phenytoin and tolbutamide but found to increase the clearance of theophylline in healthy subjects[45, 46]. Our results suggest that diclofenac does not affect theophylline metabolism when the two drugs are used together.

In conclusion, famotidine or diclofenac did not affect the pharmacokinetics of theophylline thus requiring no dose adjustment when given concomitantly.

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